Billing Code: 4160-90-M

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Agency for Healthcare Research and Quality**

**Supplemental Evidence and Data Request on Opioid Treatments for Chronic Pain**

**AGENCY:** Agency for Healthcare Research and Quality (AHRQ), HHS.

**ACTION:** Request for Supplemental Evidence and Data Submissions.

**SUMMARY:** The Agency for Healthcare Research and Quality (AHRQ) is seeking scientific information submissions from the public. Scientific information is being solicited to inform our review on *Opioid Treatments for Chronic Pain*, which is currently being conducted by the AHRQ's Evidence-based Practice Centers (EPC) Program. Access to published and unpublished pertinent scientific information will improve the quality of this review.

**DATES:** *Submission Deadline* on or before **[INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]**.

**ADDRESSES:**

*E-mail submissions:* epc@ahrq.hhs.gov.

*Print submissions*:

Mailing Address:

Center for Evidence and Practice Improvement

Agency for Healthcare Research and Quality

ATTN: EPC SEADs Coordinator

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**FOR FURTHER INFORMATION CONTACT:**

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**SUPPLEMENTARY INFORMATION:**

The Agency for Healthcare Research and Quality has commissioned the Evidence-based Practice Centers (EPC) Program to complete a review of the evidence for *Opioid Treatments for Chronic Pain*. AHRQ is conducting this systematic review pursuant to Section 902(a) of the Public Health Service Act, 42 U.S.C. 299a(a).

The EPC Program is dedicated to identifying as many studies as possible that are relevant to the questions for each of its reviews. In order to do so, we are supplementing the usual manual and electronic database searches of the literature by requesting information from the public (e.g., details of studies conducted). We are looking for studies that report on *Opioid Treatments for Chronic Pain*, including those that describe adverse events. The entire research protocol is available online at:

https://effectivehealthcare.ahrq.gov/topics/opioids-chronic-pain/protocol

This is to notify the public that the EPC Program would find the following information on Opioid Treatments for Chronic Pain helpful:

- A list of completed studies that your organization has sponsored for this indication. In the list, please *indicate whether results are available on ClinicalTrials.gov along with the ClinicalTrials.gov trial number*.
    - *For completed studies that do not have results on ClinicalTrials.gov*, please provide a summary, including the following elements: study number, study period, design, methodology, indication and diagnosis, proper use instructions, inclusion and exclusion criteria, primary and secondary outcomes, baseline characteristics, number of patients screened /eligible /enrolled /lost to follow-up /withdrawn /analyzed, effectiveness/efficacy, and safety results.
- *A list of ongoing studies that your organization has sponsored for this indication*. In the list, please provide the ClinicalTrials.gov trial number or, if the trial is not registered, the protocol for the study including a study number, the study period, design, methodology, indication and diagnosis, proper use instructions, inclusion and exclusion criteria, and primary and secondary outcomes.
- Description of whether the above studies constitute ALL Phase II and above clinical trials sponsored by your organization for this indication and an index outlining the relevant information in each submitted file.

Your contribution will be very beneficial to the EPC Program. Materials submitted must be publicly available or able to be made public. Materials that are considered confidential; marketing materials; study types not included in the review; or information on indications not included in the review cannot be used by the EPC Program. This is a voluntary request for information, and all costs for complying with this request must be borne by the submitter.

The draft of this review will be posted on AHRQ's EPC Program website and available for public comment for a period of 4 weeks. If you would like to be notified when the draft is posted, please sign up for the e-mail list at: https://www.effectivehealthcare.ahrq.gov/email-updates.

*The systematic review will answer the following questions. This information is provided as background. AHRQ is not requesting that the public provide answers to these questions.*

The Key Questions:

Key Question 1. Effectiveness and Comparative Effectiveness

a. In patients with chronic pain, what is the effectiveness of opioid therapy versus placebo or no opioid therapy for outcomes related to pain, function, and quality of life, after short-term follow-up (up to 6 months), intermediate-term follow-up (6 to 12 months), and long-term follow-up (at least 1 year)?
b. How does effectiveness vary depending on:
    (1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including low back pain], visceral pain,

fibromyalgia, sickle cell disease, inflammatory pain, headache disorders, and degree of nociplasticity);

(2) patient demographics (e.g., age, race, ethnicity, gender, socioeconomic status);

(3) patient comorbidities (including past or current alcohol or substance use disorders, mental health disorders, medical comorbidities and high risk for opioid use disorder);

(4) the mechanism of action of opioids used (e.g., pure opioid agonists, partial opioid agonists such as buprenorphine or drugs with mixed opioid and nonopioid mechanisms of action such as tramadol or tapentadol)?

c. In patients with chronic pain, what is the comparative effectiveness of opioids versus nonopioid therapies (pharmacologic or nonpharmacologic, including marijuana) on outcomes related to pain, function, and quality of life, after short-term follow-up (up to 6 months), intermediate-term follow-up (6 to 12 months), and long-term follow-up (at least 1 year)?

d. In patients with chronic pain, what is the comparative effectiveness of opioids plus nonopioid interventions (pharmacologic or nonpharmacologic, including marijuana) versus opioids or nonopioid interventions alone on outcomes related to pain, function, quality of life, and doses of opioids used, after short-term follow-up (up to 6 months),

intermediate-term follow-up (6 to 12 months), and long-term follow-up (at least 1 year)?

Key Question 2. Harms and Adverse Events

a. In patients with chronic pain, what are the risks of opioids versus placebo or no opioid on:
   (1) substance misuse, substance use disorder, and related outcomes;
   (2) overdose (intentional and unintentional);
   (3) other harms, including gastrointestinal-related harms, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms (e.g., depression)?

b. How do harms vary depending on:
   (1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including back pain], visceral pain, fibromyalgia, sickle cell disease, inflammatory pain, headache disorders, and degree of nociplasticity);
   (2) patient demographics;
   (3) patient comorbidities (including past or current substance use disorder or at high risk for opioid use disorder);
   (4) the dose of opioids used and duration of therapy;
   (5) the mechanism of action of opioids used (e.g., are there differences between pure opioid agonists and partial opioid agonists such as

buprenorphine or drugs with opioid and nonopioid mechanisms of action such as tramadol and tapentadol);

(6) use of sedative hypnotics;

(7) use of gabapentinoids;

(8) use of marijuana?

Key Question 3. Dosing Strategies

a. In patients with chronic pain, what is the comparative effectiveness of different methods for initiating and titrating opioids for outcomes related to pain, function, and quality of life; risk of misuse, opioid use disorder, and overdose; and doses of opioids used?

b. In patients with chronic pain, what is the comparative effectiveness of short-acting versus long-acting opioids on outcomes related to pain, function, and quality of life; risk of misuse, opioid use disorder, and overdose; and doses of opioids used?

c. In patients with chronic pain, what is the comparative effectiveness of different long-acting opioids on outcomes related to pain, function, and quality of life; and risk of misuse, opioid use disorder, and overdose?

d. In patients with chronic pain, what is the comparative effectiveness of short- plus long-acting opioids versus long-acting opioids alone on outcomes related to pain, function, and quality of life; risk of misuse, opioid use disorder, and overdose; and doses of opioids used?

e. In patients with chronic pain, what is the comparative effectiveness of scheduled, continuous versus as-needed dosing of opioids on outcomes

related to pain, function, and quality of life; risk of misuse, opioid use disorder, and overdose; and doses of opioids used?

f. In patients with chronic pain, what is the comparative effectiveness of opioid dose escalation versus dose maintenance or use of dose thresholds on outcomes related to pain, function, and quality of life?

g. In patients with chronic pain, what is the comparative effectiveness of opioid rotation versus maintenance of current opioid therapy on outcomes related to pain, function, and quality of life; and doses of opioids used?

h. In patients with chronic pain, what is the comparative effectiveness of different strategies for treating acute exacerbations of chronic pain on outcomes related to pain, function, and quality of life?

i. In patients with chronic pain, what are the effects of decreasing opioid doses or of tapering off opioids versus continuation of opioids on outcomes related to pain, function, quality of life, and withdrawal?

j. In patients with chronic pain, what is the comparative effectiveness of different tapering protocols and strategies on measures related to pain, function, quality of life, withdrawal symptoms, and likelihood of opioid cessation?

k. In patients with chronic pain, what is the comparative effectiveness of different opioid dosages and durations of therapy for outcomes related to pain, function, and quality of life; risk of misuse, opioid use disorder, and overdose?

Key Question 4. Risk Assessment and Risk Mitigation Strategies

a. In patients with chronic pain being considered for opioid therapy, what is the accuracy of instruments and tests (including metabolic and/or genetic testing) for predicting risk of misuse, opioid use disorder, and overdose?

b. In patients with chronic pain, what is the effectiveness of use of risk prediction instruments and tests (including metabolic and/or genetic testing) on outcomes related to misuse, opioid use disorder, and overdose?

c. In patients with chronic pain who are prescribed opioid therapy, what is the effectiveness of risk mitigation strategies, including (1) opioid management plans, (2) patient education, (3) urine drug screening, (4) use of prescription drug monitoring program data, (5) use of monitoring instruments, (6) more frequent monitoring intervals, (7) pill counts, (8) use of abuse-deterrent formulations, (9) consultation with mental health providers when mental health conditions are present, (10) avoidance of co-prescribing of sedative hypnotics, and (11) co-prescribing of naloxone on outcomes related to misuse, opioid use disorder, and overdose?

d. In patients with chronic pain, what is the comparative effectiveness of treatment strategies for managing patients with opioid use disorder related to prescription opioids on outcomes related to misuse, opioid use disorder, overdose, pain, function, and quality of life?

PICOTS (Populations, Interventions, Comparators, Outcomes, Timing, Settings)

| Key Question | Population | Intervention | Comparator | Outcome |
|---|---|---|---|---|
| **1a, b** | Adults (age ≥18 years) with various types of chronic pain including pregnant/breast-feeding women and patients treated with opioids for opioid use disorder<br>Key Question 1b: Subgroups: (1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including low back pain], fibromyalgia, sickle cell disease, inflammatory pain, and headache disorders); (2) patient demographics (e.g., age, race, ethnicity, gender); (3) patient comorbidities (including past or current alcohol or substance use disorders, mental health disorders, medical comorbidities and high risk for opioid use disorder) | Long- or short-acting opioids (including partial agonists and dual mechanism agents)<br><br>Exclude: Intravenous or intramuscular administration of opioids | Placebo or no opioid therapy | Pain, function, and quality of life) |

| Key Question | Population | Intervention | Comparator | Outcome |
|---|---|---|---|---|
| **1c** | Adults (age ≥18 years) with various types of chronic pain | Long- or short-acting opioids (including partial agonists and dual action medications)<br>Exclude:<br>Intravenous or intramuscular administration of opioids | Nonopioid therapies (pharmacologic [antiepileptic drugs, benzodiazepines, nonsteroidal antiinflammatory drugs, skeletal muscle relaxants, serotonin norepinephrine reuptake inhibitors, topical lidocaine, topical capsaicin, topical diclofenac, tricyclica antidepressants, acetaminophen, memantine, and marijuana/cannabis] or nonpharmacologic [noninvasive]) | Pain, function, and quality of life; doses of opioids used |
| **1d** | Adults (age ≥18 years) with various types of chronic pain | Opioids plus nonopioid interventions (pharmacologic or nonpharmacologic)<br>Exclude:<br>Intravenous or intramuscular administration of opioids | Opioids or nonopioid interventions alone, including marijuana | Pain, function, and quality of life, doses of opioids used |

| Key Question | Population | Intervention | Comparator | Outcome |
|---|---|---|---|---|
| **2a** | Adults (age ≥18 years) with various types of chronic pain<br>Key Question 2b: subgroups (1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including back pain], fibromyalgia, sickle cell disease, inflammatory pain, headache disorders); (2) patient demographics; (3) patient comorbidities (including past or current substance use disorder or at high risk for opioid use disorder); (4) the dose of opioids used; (5) the mechanisms of actions of the opioids; and (6) use of sedative hypnotics | Long- or short-acting opioids (including tapentadol, buprenorphine, and tramadol) opioids<br><br>Exclude: Intravenous or intramuscular administration of opioids | Placebo or no opioid | Substance misuse, substance use disorder and related outcomes, overdose, and other harms |
| **3a** | Adults (age ≥18 years) with various types of chronic pain | Long- or short-acting opioids (including tapentadol, buprenorphine, and tramadol) | Other opioids with different dose initiation and titration strategies | Pain, function, and quality of life; doses of opioids used |

| Key Question | Population | Intervention | Comparator | Outcome |
|---|---|---|---|---|
| **3b** | Adults (age ≥18 years) with various types of chronic pain | Short-acting opioid | Long-acting opioid | Pain, function, and quality of life; risk of misuse, opioid use disorder, overdose and other harms; doses of opioids used |
| **3c** | Adults (age ≥18 years) with various types of chronic pain | Long-acting opioid | Other long-acting opioid | Pain, function, and quality of life; risk of misuse, opioid use disorder, and overdose and other harms; doses of opioids used |
| **3d** | Adults (age ≥18 years) with various types of chronic pain | Short and long acting opioid | Long-acting opioid | Pain, function, and quality of life; risk of misuse, opioid use disorder, overdose and other harms; doses of opioids used |
| **3e** | Adults (age ≥18 years) with various types of chronic pain | Scheduled, continuous dosing | As-needed dosing | Pain, function, and quality of life; risk of misuse, opioid use disorder, overdose, and other harms; doses of opioids used |
| **3f** | Adults (age ≥18 years) with various types of chronic pain | Opioid dose escalation | Dose maintenance or use of dose thresholds | Pain, function, and quality of life |
| **3g** | Adults (age ≥18 years) with various types of chronic pain | Opioid rotation | Maintenance of current opioid therapy | Pain, function, and quality of life; doses of opioids used |

| Key Question | Population | Intervention | Comparator | Outcome |
|---|---|---|---|---|
| **3h** | Adults (age ≥18 years) with various types of chronic pain and an acute exacerbation | Treatments for acute exacerbations of chronic pain | Other treatments for acute exacerbations of chronic pain | Pain, function, and quality of life |
| **3i** | Adults (age ≥18 years) with various types of chronic pain | Decreasing opioid doses or of tapering off opioids | Continuation of opioids | Pain, function, and quality of life; withdrawal and other harms (including overdose, use of illicit opioids, suicidality, and anger/violence) |
| **3j** | Adults (age ≥18 years) with various types of chronic pain | Tapering protocols and strategies | Other tapering protocols or strategies | Pain, function, quality of life, likelihood of opioid cessation, withdrawal symptoms and other harms (including overdose, use of illicit opioids, suicidality, and anger/violence) |
| **3k** | Adults (age ≥18 years) with various types of chronic pain | Dosage of opioid | Other dose of same opioid | Pain, function, and quality of life; risk of misuse, opioid use disorder, overdose and other harms |
| **4a** | Adults (age ≥18 years) with various types of chronic pain | Instruments, genetic/metabolic tests for predicting risk of misuse, opioid use disorder, and overdose | Reference standard for misuse, opioid use disorder, or overdose; or other benchmarks | Measures of diagnostic accuracy |

| Key Question | Population | Intervention | Comparator | Outcome |
|---|---|---|---|---|
| **4b** | Adults (age ≥18 years) with various types of chronic pain | Use of risk prediction instruments, genetic/metabolic tests | Usual care or other control | Misuse, opioid use disorder, overdose and other harms |
| **4c** | Adults (age ≥18 years) with various types of chronic pain | Risk mitigation strategies, including (1) opioid management plans, (2) patient education, (3) urine drug screening, (4) use of prescription drug monitoring program data, (5) use of monitoring instruments, (6) more frequent monitoring intervals, (7) pill counts, (8) use of abuse-deterrent formulations, (9) consultation with mental health providers when mental health conditions are present, (10) avoidance of benzodiazepine co-prescribing and (11) co-prescribing of naloxone | Usual care | Pain, function, quality of life, misuse, opioid use disorder, overdose and other harms (including use of illicit opioids, suicidality, and anger/violence) |
| **4d** | Adults (age ≥18 years) with various types of chronic pain and opioid use disorder | Treatment strategies | Other treatment strategies | Pain, function, quality of life, misuse, opioid use disorder, overdose, other harms, pain, function, and quality of life |

Additional Inclusion Criteria:

Timing:

- For all questions, studies with at least 1 month of followup will be included. Results will be stratified according to short-term (1 to 6 months), intermediate term (6 to 12 months), and long-term (≥1 year) followup.

Setting:

- Include: Outpatient settings (e.g., primary care, pain clinics, other specialty clinics, emergency rooms, urgent care clinics)
- Exclude: Addiction treatment settings, inpatient settings

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[FR Doc. 2019-05145 Filed: 3/18/2019 8:45 am; Publication Date: 3/19/2019]